California Medicine

Drug Treatment of Psychotic Patients in General Medical Practice

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■ *It is possible for general medical practitioners to successfully treat many psychotic patients in their offices, provided they have some training in psychiatric diagnosis and in psychotherapy procedures appropriate to the general situation of the practicing non-psychiatrist physician. This has become so because of recent developments in psychopharmacology.*

Drugs are now available which permit control of the symptoms of psychoses with reasonable specificity. The phenothiazines are appropriate for patients with schizophrenic psychoses. The "target symptoms" indicate which one to use.

The affective psychoses are best handled with dibenzazipine anti-depressants. With proper medication and frequent short supportive interviews, many such patients can be successfully treated.

RECENT ADVANCES in pharmacology have made available a large number of compounds that are very useful in the management of psychiatric patients. In some instances, notably the incipient to moderately severe psychotic states, these drugs have made it possible to treat many patients while they remain at home and on the job. Before the introduction of chlorpromazine in 1952, hospitalization was almost mandatory for the management of the psychotic patient. Psychotherapy was often impossible to attempt for some time (if ever) after the onset of the more severe psychotic states.

Developments in psychopharmacology make it possible to work with almost every patient, even those with severely disruptive psychiatric symptoms. These agents permit the physician to make communicative contact and to develop a therapeutic relationship with the patient. Physicians who are reluctant to enter such relationships will often mis-

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use the psychoactive drugs by attempting only to abolish symptoms and, with them, the demands that the patient makes on the physician. If these compounds are introduced into treatment as a substitute for an effective communicative relationship, then they are being incorrectly utilized. Therapy is far less successful, and indeed may fail, if drugs are the only vehicle of treatment. By correct use of drugs in adequate dosage and maintaining an ongoing relationship, the family physician who wishes to do so can treat many psychotic patients he encounters.

There are two necessary pre-conditions for undertaking treatment with the psychoactive drugs. The first is a good background in psychiatric diagnosis (such as may be obtained from continuing education courses in psychiatry for non-psychiatrists that are offered by several of the medical schools in California). The second is an interest in the patient as a person.

Psychotic patients who are not so disturbed as to require treatment in a hospital will be found among the patients in two groups: those with schizophrenic and those with affective psychosis. Therefore, the two classes of drugs to be considered in this article are the phenothiazines, used in the management of schizophrenic patients, and the anti-depressants. The minor tranquilizers, such as chlordiazepoxide (Librium®) and meprobamate (Miltown,® Equanil®), have no place in the treatment of psychosis.

The Phenothiazines

All of the compounds in the phenothiazine group are considered "major" tranquilizers. They are capable of reducing extreme tension or agitation and in many instances have an anti-psychotic activity. Some have demonstrated the capacity to suppress delusions and hallucinations. As a consequence they are primarily indicated for psychotic patients —rarely, if ever, in the treatment of neurosis.[3,5] In fact, most neurotic patients will become quite uncomfortable, and feel an unpleasant sense of detachment or depression if given phenothiazines.

The pharmacological action of this group includes the following: They block the sympathetic nervous system, giving rise to parasympathomimetic effects, including atropine-like activity. They have anti-histamine properties. They are all anti emetic, though to varying degrees. In large dosage they are capable of producing sedation, hypnosis and anesthesia. These dosages, however, generally are far in excess of therapeutic doses. They potentiate analgesics and anesthetics. The ability of the phenothiazines to control extreme anxiety and agitation without producing sleep is probably the result of the site of action. Unlike the barbiturates, which in general act most strongly on the cerebral cortex (thus depressing functions concerned with analyzing mechanisms of vision, audition and other perceptive functions), the phenothiazines chiefly affect the subcortical structures regarded as parts of the anatomic substrata of emotion; the midbrain reticular formation, the hypothalamus and parts of the rhinencephalon.[6]

The phenothiazines can be divided into three major subgroups. All have the phenothiazine nucleus in their chemical structure and differ only in the substituents.[4]

The *dimethyl subgroup* includes chlorpromazine (Thorazine®), promazine (Sparine®), triflupromazine (Vesprin®), and promethazine (Phenergan®). These agents are the most sedative of the phenothiazines and are therefore most useful in controlling psychotic agitation, hyperactivity and other psychotic symptoms for which a sedative tranquilizer would be desirable. They do not produce nearly the degree of sedation or hypnosis that the barbiturates would if given in sufficient amounts to control psychotic agitation. Phenergan® is often useful in promoting sleep in psychotic patients.

Chlorpromazine (Thorazine®) was first reported to be useful in the management of psychosis by Delay and his associates in 1952. Since that time it has been given to an estimated 50 million patients.[2] Although at first it was hoped that chlorpromazine would cure psychiatric disorders, it is now clear that its major value is that it ameliorates certain symptoms in both acute and chronic schizophrenic disorders. It is not indicated in the neurotic disorders. The accumulated experience of many clinicians indicates that withdrawn, inactive patients or patients with blunted or dulled affect will be helped very little, if at all, by chlorpromazine. The most useful role of this drug is in the management of severely anxious, disturbed or overactive (excited) schizophrenic patients. The dosage will vary from 300 mg a day to as high as 2,000 mg a day, depending on the severity of the symptoms. After control of symptoms is achieved and maintained for several months, the dose can slowly be reduced until the amount needed for maintenance is found. If this is larger than 200 to 400 mg a day, it will be necessary to concomitantly administer an anti-parkinsonism drug such as *benztropine* (Cogentin®), *trihexyphenidyl* (Artane®) or *procyclidine* (Kemadrin®), since extrapyramidal reactions are very common at that dosage level and above.

There is no clinical evidence for tolerance or addiction. Chlorpromazine has been discontinued after years of administration without withdrawal symptoms. Side-effects are relatively few. The incidence of jaundice is less than 0.5 per cent. The incidence of agranulocytosis is approximately 1 in 250,000 cases. When jaundice occurs, it is most

likely to occur in the first month of treatment. Thereafter it is very unlikely. Fatalities from chlorpromazine-induced hepatitis are very rare. Only six reports involving 14 cases appear in the world medical literature. Chlorpromazine has been given to many pregnant women without harm to mother or infant.[2]

Promazine (Sparine®) is a drug which has proven to be especially useful in the lesser degrees of psychotic agitation, senile agitation and agitation during withdrawal from alcohol. The usual dosage is 100 to 200 mg a day, divided into four doses. At this dosage level, extrapyramidal effects are rarely seen.

The *piperidyl subgroup* contains only one useful compound. This is thioridazine (Mellaril®). It is used in the same situations as the dimethyl subgroup. It is probably the most sedative of the phenothiazines. In my experience, it is particularly useful in controlling the acute manic state. Despite manufacturer's claims to the contrary, with doses over 200 mg a day, extrapyramidal side-effects are common. Control of an acutely excited, overactive or agitated psychotic patient is rarely achieved on less than 150 mg a day; 200 to 300 mg a day is the more usual necessary dose.

The major pharmacological difference between thioridazine and chlorpromazine are that the latter has lower anti-emetic activity, less adrenergic blocking and less interference with temperature regulation. The effective dose of thioridazine is far smaller than of chlorpromazine. This may account for the fact that with this drug some clinicians have reported control of schizophrenic symptoms with fewer and milder extrapyramidal side-effects than seen with some other phenothiazines.

The third subgroup, the *piperazine phenothiazines,* are the most potent, milligram for milligram, and the least sedative. They are therefore most useful in those psychotic conditions in which apathy and withdrawal are prominent. They are more likely to be effective in the emotionally blunted patient than chlorpromazine or thioridazine. Unlike the other two groups, they are not contraindicated in depressed psychotic patients, although depression does not respond favorably to the administration of phenothiazines. Because of their potency, side-effects are more frequent and more pronounced than with either of the other two subgroups. Extrapyramidal symptoms are almost invariably produced if dosages sufficient to be therapeutically active are given. These drugs should therefore be given together with an anti-parkinsonism preparation. The piperazine compounds often suppress delusions and hallucinations in schizophrenic patients. Chlorpromazine and thioridazine rarely suppress chronic delusions and hallucinations, although the patient may be relatively unconcerned about them.

The chief representatives of this group are fluphenazine (Prolixin,® Permitil®), trifluoperazine (Stelazine®), perphenazine (Trilafon®), and prochlorperazine (Compazine®). In my experience, the two latter drugs produce extrapyramidal phenomena more than any other of the phenothiazines. However, all phenothiazines do, to some extent. But because of this, fluphenazine (Prolixin®) and trifluperazine (Stelazine®) appear to be the drugs of choice for chronic, withdrawn, apathetic schizophrenic patients, particularly when delusions and hallucinations are prominent.

The Anti-Depressants

The anti-depressants fall into two groups, the mono-amine oxidase inhibitors (so-called MAO inhibitors) and the dibenzazipine derivatives. The MAO inhibitors have a stimulant effect of relatively short duration on the central nervous system. They are frequently very effective as anti-depressants but have sufficient disadvantages to warrant great caution in their use.[1] They can have serious toxic effects on the liver, with resultant jaundice. Death from liver toxicity has been reported. They are slow in onset of action and difficult to regulate. All MAO inhibitors may cause tremors, overstimulation and insomnia. Hypotensive side-effects must be watched for. The hydrazine MAO inhibitors include iproniazid (Marsilid®), phenelzine (Nardil®), nialamide (Niamid®), and isocarboxazid (Marplan®). In agitated depressions, or in depressed patients with anxiety, the MAO inhibitors are not the drugs of choice and often will increase anxiety or tension. MAO inhibitors may dangerously potentiate anesthetic agents, ganglion blockers, atropine, morphine, meperidine (Demerol®) and other narcotic agents, as well as anti-malarial drugs.

The dibenzazipine derivatives are more akin to the phenothiazine compounds than to the MAO inhibitors. Chemically, the dibenzazipine nucleus is very similar to the phenothiazine nucleus. The drugs have an inhibitory or suppressant central nervous system effect. The electroencephalographic pattern after administration of these drugs is similar to that produced by phenothiazines. These drugs are especially useful in agitated depressions.

Imipramine (Tofranil®) has had extensive use. It is often effective in severe depressions with agitation. Its effect is slow, and depression may not begin to lift for seven to twenty-eight days after administration has begun. Side-effects are frequent and pronounced. They include flushing, excessive perspiration, dry mouth, constipation and postural

hypotension. The patient should be warned about these effects, lest he discontinue taking the drug.

Amitriptyline (Elavil®) is chemically and pharmacologically very similar. Side-effects are far less severe, however, and its action is not as slow as that of imipramine, although each seems to help some patients with severe depressive states who are not helped by the other. The dosages are similar, 75 to 100 mg daily. Amitriptyline is often successful in controlling agitation in depressed patients. Most patients will complain of drowsiness for two or three days after administration is begun. Dry mouth is common.

In order to find an effective anti-depressant, it may be necessary to try several different ones. However, if the physician plans to discontinue one type and use a drug of another type, he should interrupt medication for two weeks if he is discontinuing an MAO inhibitor, and for at least three weeks if he is discontinuing impramine or amitriptyline in order to try an MAO inhibitor.

The physician who will spend sufficient time with his patients can, with training obtainable in continuing education programs such as the one offered at the University of Southern California, recognize and treat many psychotic persons. With good management, hospitalization can be very brief or in many instances not necessary. What patients of this kind need is proper medication and frequent supportive interviews. The interviews should not be the traditional 50-minute hour of the psychotherapist. In our advanced clinic courses at U.S.C. School of Medicine for non-psychiatrist physicians, many psychotic patients are being successfully treated with drugs and psychotherapy sessions of 15 to 25 minutes at intervals of seven to fourteen days. This approach is applicable to the practice of almost any family physician.

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